CLAIMS

[1] A hyaluronic acid-methotrexate conjugate, wherein methotrexate is conjugated with a carboxyl group of hyaluronic acid, a hyaluronic acid derivative, or a salt thereof through a linker containing a peptide chain consisting of 1 to 8 amino acids.

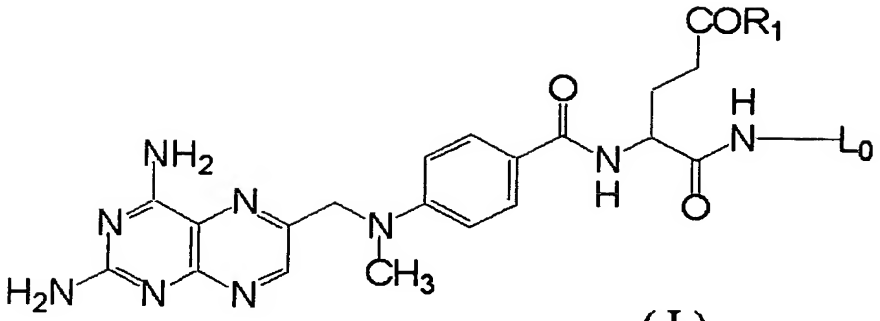
[2] The hyaluronic acid-methotrexate conjugate according to claim 1, wherein the linker contains a peptide chain consisting of 1 to 8 amino acids and a C_{2-20} alkylenediamine chain, wherein the alkylenediamine chain optionally has 1 to 5 oxygen atoms inserted thereinto and/or is optionally substituted by a carboxyl group or a C_{1-6} alkoxycarbonyl group.

[3] The hyaluronic acid-methotrexate conjugate according to claim 1 or 2, wherein the conjugation rate of methotrexate is 0.5% to 4.5% based on the total carboxyl groups of hyaluronic acid.

[4] The hyaluronic acid-methotrexate conjugate according to any one of claims 1 to 3, wherein the molecular weight of hyaluronic acid is 600,000 daltons or more.

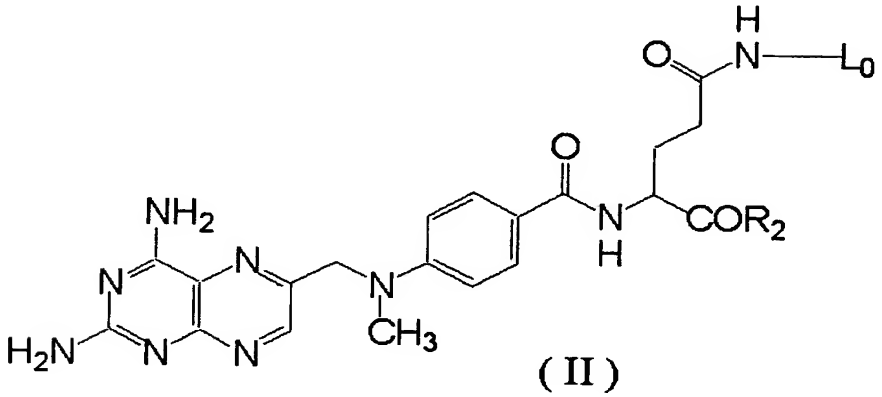
[5] The hyaluronic acid-methotrexate conjugate according to any one of claims 1 to 4, wherein methotrexate conjugated with the linker is represented by formula (I), (II), (III), or (IV):

[Formula 1]



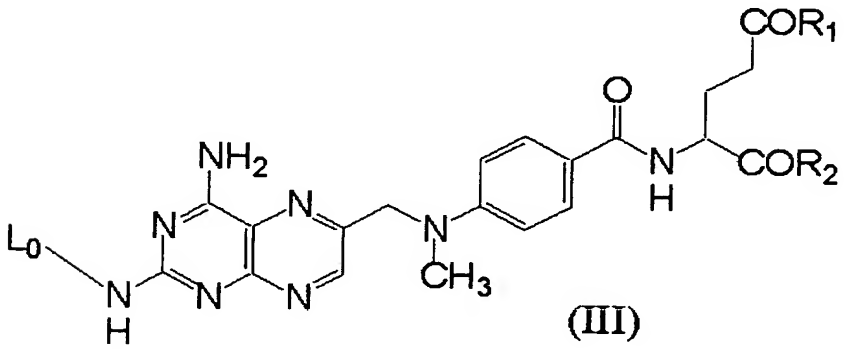
(I)

[Formula 2]



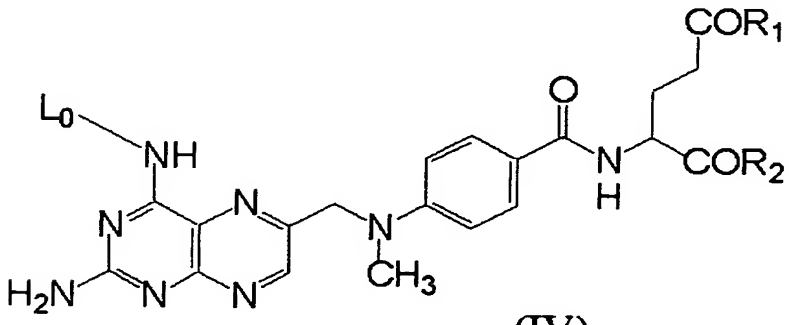
(II)

[Formula 3]



(III)

[Formula 4]



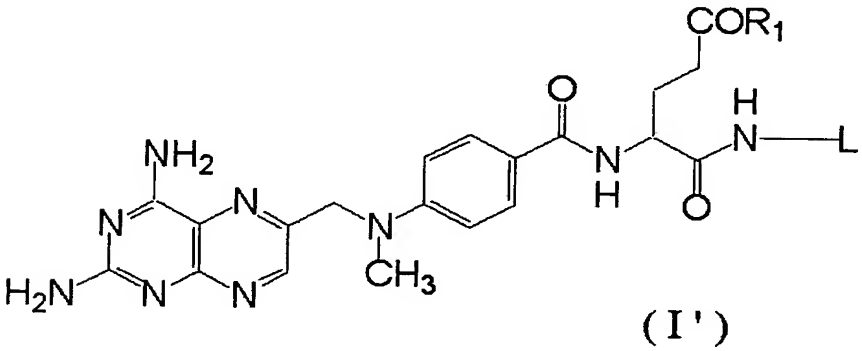
(IV)

wherein R_1 and R_2 are each independently a hydroxy group, an amino group, a C_{1-6} alkoxy group, a C_{1-6} alkylamino group, or a di-C_{1-6} alkylamino group;

L_0 is the conjugation position of the linker.

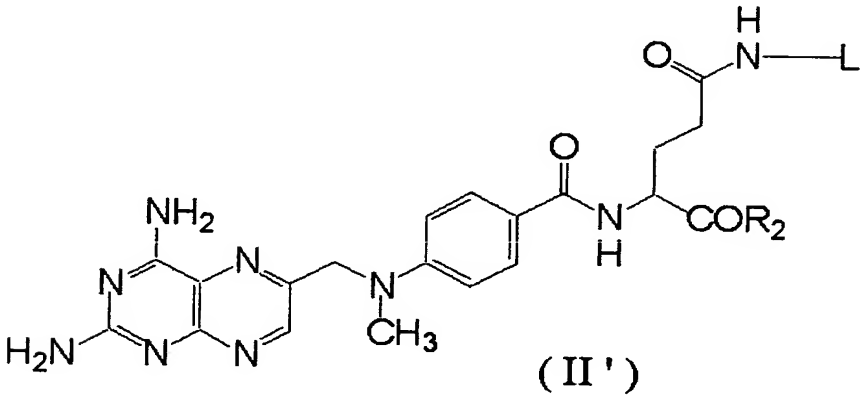
[6] The hyaluronic acid-methotrexate conjugate according to any one of claims 1 to 4, wherein the linker containing a peptide chain and methotrexate conjugated with the linker is represented by formula (I') or (II'):

[Formula 5]



(I')

[Formula 6]

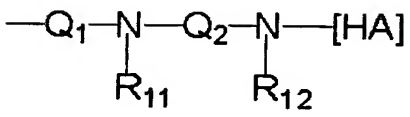


(II')

wherein R_1 and R_2 are each independently a hydroxy group, an amino group, a C_{1-6} alkoxy group, a C_{1-6} alkylamino group, or a di-C_{1-6} alkylamino group;

L is a linker represented by formula (X):

[Formula 7]



(X)

wherein Q_1 forms, together with -NH- binding thereto, a peptide chain consisting of 1 to 8 amino acids; residues of amino acids contained in the peptide chain are each independently optionally substituted or protected by one or more groups selected from the group consisting of a C_{1-6} alkyl group, a C_{1-6} alkylcarbonyl group, a C_{1-6} alkoxycarbonyl group, a formyl group, a C_{1-6} alkylsulfonyl group, and a C_{6-10} arylsulfonyl group; amide bonds contained in the peptide chain are each independently optionally substituted on the nitrogen atom by one or more C_{1-6} alkyl groups and/or C_{1-6} alkylcarbonyl groups; and carboxyl groups contained in the residues are each independently optionally converted to an amide group optionally substituted by one or two C_{1-6} alkyl groups;

R_{11} and R_{12} are each independently a hydrogen atom or a C_{1-6} alkyl group;

Q_2 is C_{2-20} alkylene, wherein the alkylene optionally has 1 to 5 oxygen atoms inserted thereinto and/or is optionally substituted by a carboxyl group or a C_{1-6} alkoxycarbonyl group; and

[HA] represents the position of conjugation with hyaluronic acid, and the linker forms an amide bond with a carboxyl group contained in the hyaluronic acid.

[7] A pharmaceutical composition containing the

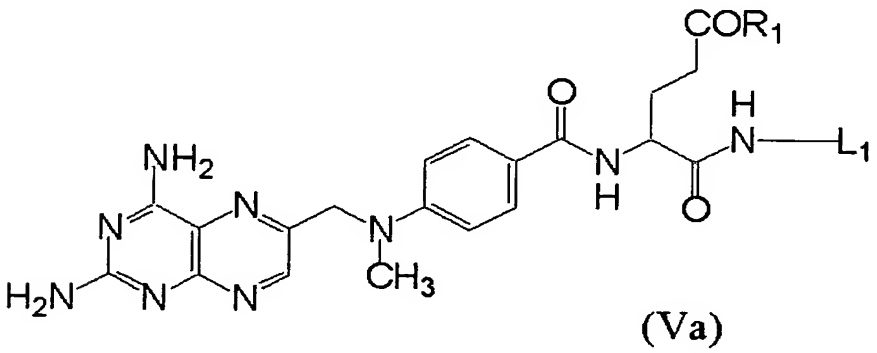
hyaluronic acid-methotrexate conjugate according to any one of claims 1 to 6 as an active ingredient.

[8] A therapeutic drug for joint diseases, containing the hyaluronic acid-methotrexate conjugate according to any one of claims 1 to 6 as an active ingredient.

[9] The therapeutic drug for joint diseases according to claim 8, which is a topical preparation for administration into the joint.

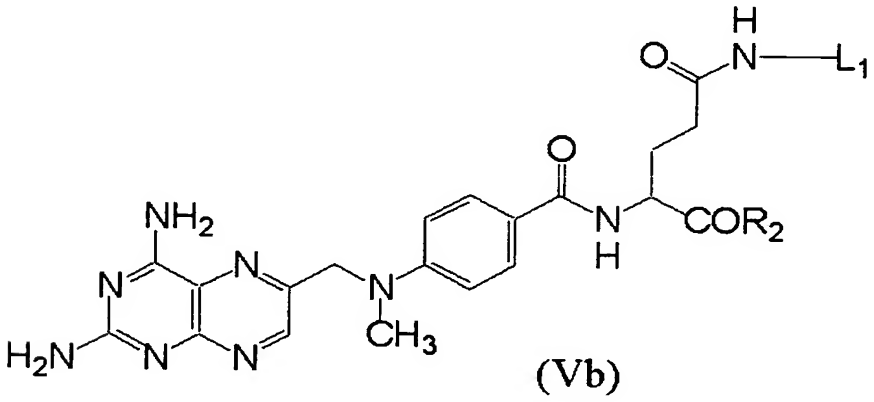
[10] A compound of formula (Va) or (Vb):

[Formula 8]



(Va)

[Formula 9]

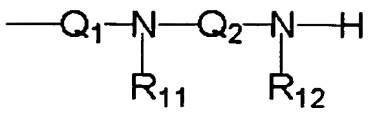


(Vb)

wherein R_1 and R_2 are each independently a hydroxy group, an amino group, a C_{1-6} alkoxy group, a C_{1-6} alkylamino group, or a di-C_{1-6} alkylamino group;

L_1 is a linker represented by formula (X'):

[Formula 10]



(X')

wherein Q_1 forms, together with -NH- binding thereto, a peptide chain consisting of 1 to 8 amino acids; residues of amino acids contained in the peptide chain are each independently optionally substituted or protected by one or more groups selected from the group consisting of a C_{1-6} alkyl group, a C_{1-6} alkylcarbonyl group, a C_{1-6} alkoxycarbonyl group, a formyl group, a C_{1-6} alkylsulfonyl group, and a C_{6-10} arylsulfonyl group; amide bonds contained in the peptide chain are each independently optionally substituted on the nitrogen atom by one or more C_{1-6} alkyl groups and/or C_{1-6} alkylcarbonyl groups; and carboxyl groups contained in the residues are each independently optionally converted to an amide group optionally substituted by one or two C_{1-6} alkyl groups;

R_{11} and R_{12} are each independently a hydrogen atom or a C_{1-6} alkyl group; and

Q_2 is a C_{2-20} alkylene, wherein the alkylene optionally has 1 to 5 oxygen atoms inserted thereinto and/or is optionally substituted by a carboxyl group or a C_{1-6} alkoxycarbonyl group.

[11] A process for producing the hyaluronic acid-methotrexate conjugate according to claim 1, which comprises the steps of reacting the compound of formula

(Va) or (Vb) according to claim 10 with hyaluronic acid and converting a carboxyl group of the hyaluronic acid to an N-substituted amide group.